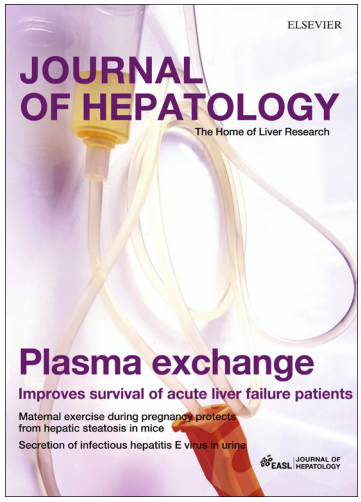

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Exercise in NAFLD: Just do it.

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The health burden of non-alcoholic fatty liver disease (NAFLD) is multifaceted. In addition to sequelae of end-stage liver disease and hepatocellular carcinoma, the deleterious role of hepatic steatosis in the development of type 2 diabetes and cardiovascular disease is also well established.(1,2) NAFLD affects up to one third of the adult population and may become more prevalent with the escalation of obesity globally. Therefore, there is an urgent need for effective therapies for not only reducing steatosis and liver injury, but for improving insulin resistance and the cardiovascular risk associated with NAFLD.

Although there are many promising drug therapies in phase II and III clinical trials, treating a large proportion of the population with medications for many years will be an expensive management option at a population level. As there are no pharmacological agents currently accepted for the long-term treatment of NAFLD, the mainstay of treatment is weight loss via lifestyle intervention incorporating dietary and structured exercise intervention.(3) Indeed, weight gain is arguably the strongest determinant of the development of NAFLD (4), and weight loss is the greatest predictor of reductions in liver fat and aminotransferases.(3) Even small reductions (3-5% body weight loss) reduce steatosis and associated metabolic parameters however, larger reductions (≥10%) appear to be required for histologic improvements of liver injury.(5) Whilst weight loss is effective, it is notoriously difficult to sustain in the long term.(6) Exercise is routinely recommended for the management of NAFLD, since the efficacy of exercise *per se* for the reduction of liver fat is now recognized (7), and exercise has a multiplicity of benefits beyond weight loss. While questions regarding the optimal 'dose' of exercise therapy for reducing liver fat have been the focus of recent clinical investigations, consensus as to how effective exercise is over a longer term at a population level is unclear. Furthermore, how much exercise is required to prevent or

reverse NAFLD has remained elusive. This is in part due to the paucity of epidemiological data to support the findings of smaller clinical trials.

In this issue of the *Journal of Hepatology,* Sung and colleagues examine the association between exercise with both incident NAFLD and the resolution of NAFLD in a large cohort of adults followed over a mean of five years (8). This paper provides the first longitudinal epidemiological data to support the utility of exercise in both the prevention and treatment of NAFLD. Within the setting of an occupational health screening program, 169,347 men and women had repeat measures of liver fat (quantified with ultrasound) and physical activity. Of the 126,811 adults at baseline without NAFLD, 23% developed NAFLD at follow up and displayed an adverse cardiovascular risk profile when compared with participants who remained free from NAFLD. Of the 42,536 individuals with NAFLD at baseline, 34% of cases resolved. After adjusting for potential confounders, including change in body mass index (BMI), any level of moderate-vigorous exercise was associated with both a reduced risk of incident NAFLD and with the resolution of NAFLD. The greatest benefits were observed with exercise frequency ≥5 days per week, with a 16% reduction in NAFLD incidence and 40% increase in NAFLD resolution over the follow-up. Higher levels of exercise at baseline and increasing the frequency of weekly exercise bouts over time were also associated with a lower risk of incident NAFLD and the resolution of NAFLD.

These data have evident clinical ramifications with the authors concluding that weekly exercise of moderate-vigorous intensity independently reduces the risk of developing NAFLD, and improves the resolution of existing NAFLD. Noteworthy limitations were the diagnosis of NAFLD via ultrasound, which has limited ability to detect smaller changes in liver steatosis, the lack of dietary data and the assessment of exercise by the Korean version

of the International Physical Activity Questionnaire Short Form. This self-report method, which recalls physical activity behavior over a seven-day period, is prone to self-report bias and typically leads to an overestimation of physical activity levels. Nevertheless, a dose-response relationship was observed between reported exercise frequency and protection from incident NAFLD as well as future NAFLD resolution, suggesting a true 'causal' relationship. However, the IPAQ questionnaire assessment is only semi-quantitative and thus the ability of the study to determine the optimal prescriptive 'dose' of exercise (encompassing the frequency, intensity, duration and type of exercise) is limited.

This information gap is filled in part, by smaller, short-term, randomized controlled trials (RCT's) examining the efficacy of exercise for the reduction of liver fat. Multiple studies examining aerobic exercise, typically comprising 30-60 minutes of moderate to vigorous exercise on 3-5 days per week, have consistently demonstrated benefits with mean 10-44% relative reductions in intrahepatic lipid by magnetic resonance spectroscopy.(7) Notably, a recent RCT demonstrated no difference between low volume high-intensity and high volume low-intensity aerobic exercise, in reducing hepatic steatosis, suggesting different combinations of aerobic exercise may be equally beneficial.(9) In addition to reducing liver fat, these doses of exercise have clear extra-hepatic benefits including improvements in comorbid insulin resistance, systemic inflammation, dyslipidaemia, hypertension and endothelial dysfunction.(10) Thus, the well-established protective effect of physical activity on cardiovascular morbidity and mortality in the general population is likely to be applicable to patients with NAFLD.(11) Given that cardiovascular disease remains the leading cause of death in NAFLD patients, encouraging regular exercise should be advocated independently of its effect on liver disease.

Benefits are also seen with resistance-based exercise, although the evidence for resistance-based exercise for reducing steatosis is less consistent with large heterogeneity in the dose of resistance training employed. Whether resistance training is as efficacious in reducing hepatic fat as aerobic exercise is unclear, with one small RCT demonstrating no difference between interventions whereas a larger trial over 8 months favoured aerobic exercise.(12,13) However, resistance training improves insulin sensitivity, muscle strength and function, which are important given the recently demonstrated association between sarcopenia and risk of NAFLD.(14) In accordance with clinical recommendations for resistance exercise in cardiovascular disease risk modification, the current evidence suggests that resistance training should complement, rather than replace, aerobic exercise training.(15)

As exercise has been convincingly demonstrated to reduce hepatic steatosis, improve liver enzymes and ameliorate insulin resistance, it would be anticipated that it might also improve liver inflammation and injury in patients with NAFLD. Cross-sectional data from NAFLD patients undergoing liver biopsy, suggests that individuals who reported engaging in vigorous-intensity exercise have a lower BMI-adjusted odds for non-alcoholic steatohepatitis (NASH) and advanced fibrosis.(16) However, there are no clinical trials examining optimal doses of exercise that reverse liver injury and fibrosis. Moreover, while lifestyle intervention resulting in >7-10% weight loss has been associated with a reduction in liver injury and fibrosis (6), there is currently no evidence to suggest that exercise in isolation without concomitant weight loss can reduce NASH or fibrosis. Thus there is a need to determine the interaction between exercise and NASH, fibrosis and the associated metabolic outcomes, as well as the added benefits of exercise atop of weight loss for liver-related outcomes. A major limitation for research in this field is the invasive nature of liver

biopsy, which is not palatable for the majority of patients. Thus, future population studies incorporating non-invasive assessment of fibrosis such as transient elastography or non-invasive markers are eagerly awaited.

The large sample size included in Sung and colleagues work allows for a well-powered analysis of free-living individuals at a population level, and thus considerably strengthens the consensus that exercise is effective as a prevention and treatment strategy for NAFLD. This study also reinforces that NAFLD is a dynamic condition, with one-third of the 42,536 individuals with fatty liver at baseline having resolution after five years. Resolution was associated with a modest mean reduction in BMI (-0.5 kg/m^2) and increase in the number of weekly exercise sessions. Thus, relatively modest weight reduction in conjunction with increased exercise frequency has the potential to significantly impact on the prevalence of NAFLD at a population level. While most successful lifestyle interventions will be multidisciplinary (including dietitians, exercise specialists and psychologists), these findings highlight that emphasis should be placed on exercise adoption and maintenance in the primary management of NAFLD. Patients with NAFLD have been shown to understand the 'benefits of exercise' however don't participate due to low confidence and a fear of falling, highlighting the need for strategies to overcome these barriers.(17) Promising therapies include high intensity interval training (HIIT) with a recent study employing a modified HIIT protocol (combined aerobic and resistance exercise) demonstrating significant reductions in steatosis and improved cardiac function.(18) Pilot studies examining acceleration training (resistance exercise performed on a vibration platform) and hybrid training (involving the voluntary and electrical contraction of muscles) demonstrate the potential for innovative strategies to also improve liver fat in NAFLD.(19,20)

While further research will enable clinicians to titrate the dose required for individual benefit across the spectrum of NAFLD, there is now clear consensus that exercise is a 'polypill' for the management of NAFLD; we just need to learn how to get patients to take it regularly and seriously.

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